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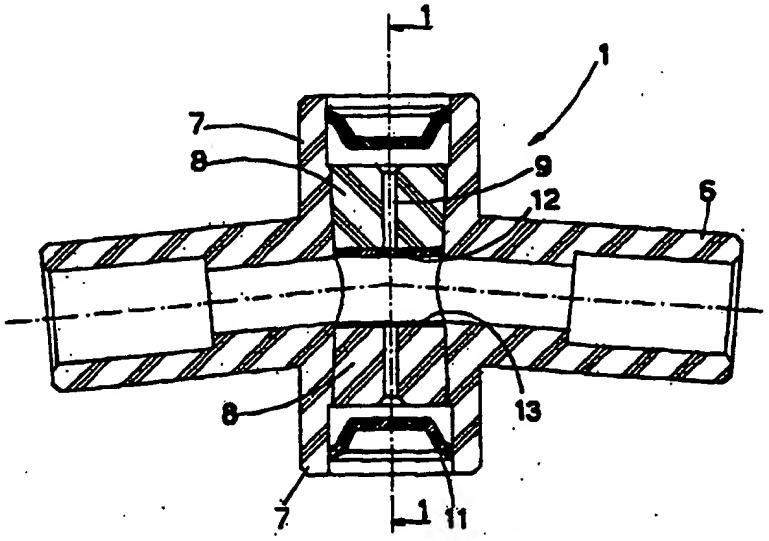
(54) Title: SENSOR FOR MONITORING IONIC ACTIVITY IN BIOLOGICAL FLUIDS



(57) Abstract

The invention relates to the field of biomedical apparatus for determining ionic activity in a biol gical fluid, and comprises a plastic tube (6) in which a sensor (12) is inserted, said sensor (12) being suitable for reading ionic activity in a fluid passing through the tube (6). Two electrodes (10) are inserted in the tube (6), one of which is connected to the sensor (12) while the ther is in direct contact with the fluid. The electrodes (10) are connected to a data processing unit which transforms electrical signals into numerical values and visualizes them in alphanumeric and/or graphic form. The invention also relates to a process for realizing the sensor (12), in the form of a membrane obtained by evaporation of a PVC solution in which a carrier matrix f r a determined ion is also inserted.

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Sensor for Monitoring Ionic Activity in Biological Fluids

Description.

The invention relates to a biomedical monitoring apparatus comprising a disposable sensor for monitoring ionic activity in biological fluids and a process for obtaining the sensor.

In the biomedical field, and especially in the field of dialysis, it is essential to identify both presence and quantities of ions of chemical elements in diluted biological fluids such as blood, and in recent years much effort has been expended in the search for improvements in monitoring apparatus for the purpose.

Up until now, determining ionic activity, that is, assessing the concentration of one or more ions in a fluid, is performed in a laboratory after having drawn a quantity of the fluid to be analyzed at predetermined time intervals, with considerable discomfort on the part of the patient.

Present laboratory techniques do not provide instantaneous answers, which may be necessary in certain circumstances as well as in some

pathological states, where the doctor needs results fast in order to be able to proceed to a cure or therapy.

A principal aim of the present invention is to quantify one or more ions in a biological fluid in real time as well as continuously during treatment, such as dialysis, on an individual patient. With the invention, the doctor can follow the activity of the ion on a monitor, and can record the results so that later a comparison can be made with other results and a full pathology documented.

A further aim of the invention is to provide an apparatus which can rapidly be calibrated according to the type of ion to be assessed, the calibration being done only once and before commencing a treatment.

A still further aim of the invention is to provide a stable sensor, guaranteeing a uniform signal overall during a therapy.

These and other aims besides are all achieved by the present invention, which is characterised as in the accompanying claims.

Further characteristics and advantages of the present invention will better emerge from the

detailed description that follows, of an embodiment of the invention, illustrated in the form of a non-limiting example in the accompanying drawings, in which:

- Figure 1 shows a longitudinal section of a conduit insertable in a circulation circuit of a fluid, and bearing a sensor for ionic activity;
- figure 2 shows the conduit according to section 1-1 of figure 1;
- figure 3 schematically shows the totality of components which make up the apparatus.

With reference to figure 3, the apparatus comprises a dedicated part, denoted by 1, which is inserted between a fluid inlet conduit 2 and a fluid outlet conduit 3 through which flows a liquid containing a determined quantity of ions, and also comprises a data processing unit 4 receiving electrical signals coming from the dedicated part through two electrical conductors 5.

As can be seen in figures 1 and 2, the dedicated part 1 is constituted by a section of plastic tube 6, advantageously made in stiff PVC, which is provided with two projections 7 through which a single through-hole is made. Two conical plugs

made in the same material as the plastic tube 6 are inserted in the two ends of the through-hole. Each plug is provided with a central through hole 9 in which an electrode 10 is inserted, made of a specially treated metal such as silver chloride. On its lower surface facing the central through-hole of the plastic tube 6, the upper plug 8 bears a membrane 12 constituting a sensor. The disposable sensor 12 monitors the activity of one or more ions.

The manufacturing process of the sensor 12 will be described hereinafter.

The projection throgh-hole 9 is closed at either end by sunk contacts 11 forced along the walls of the projections up until they contact with the electrodes 10.

In more detail, the upper metal electrode 10a is inserted between the sensor 12 and the upper contact, while the lower metal electrode 10b touches the lower contact and penetrates into the plastic tube 6 hole sufficiently deeply to contact with an inert membrane 13, such that both the membranes 12 and 13 are in contact with the liquid to be analyzed.

The tube segment constituting the dedicated part 1

can be sterilized according to normal standard procedures.

In the dedicated part, following the passage of biological fluid containing unknown ions, a millivolt electrical signal is generated, the numeric value of which is correlated to the ionic activity in the fluid, which signal is then sent to the data processing unit to be collected, memorized and processed in order to be translated into a numeric value, and which is then visualized in alphanumeric and/or graphic form.

In the illustrated embodiment reference is made to two only projections 7 with two electrodes 10 and one only sensor 12, though it is evident that further couples of projections could be provided along the plastic tube 6, together with electrodes and sensors for reading various ions, without having to modify the invention significantly.

The process for obtaining the sensor 12 will now be described.

The process is based on the preparation of a solution for a certain quantity of PVC powder in a solvent suitable not only for PVC but also for an additive carrier matrix solution. When the PVC solution is ready, it is poured in an evaporation

dish and left until it has completely evaporated. Thus a membrane or film is obtained which can be removed from the dish and packed in card in a dark room.

Various methods can be used to mount the membrane on the lower face of the plug, for example by cutting the film into discs which can then be cemented on to the plug. The membrane can also be directly formed on the plug, if so desired.

To obtain the above, a determined volume of the solution can be poured directly on to the plugs, which are specially prepared so that the solution does not drip off them during the hardening process.

The above-described process, though relatively rather long to achieve, obviates thermal stress on the membranes, which therefore last longer and are more stable.

Now a practical and non-limiting example of the process will be described, for making a film which will be sensitive to the sodium ion.

The following are poured into a hermetically-sealable glass container:

1) two millilitres of a suitable solvent for all the components which will make up the film, viz:

2) two hundred microlitres of matrix solution with the additive (5mg/ml);

3) close, shake, reopen;

4) two hundred microlitres of carrier matrix solution (50 mg/ml);

5) add one millilitre of solvent;

6) close, shake, reopen;

7) add one hundred and sixty eight microlitres of PVC plasticizer;

8) due millilitres of solvent;

9) close, shake, reopen;

10) sprinkle two hundred mg. of PVC powder;

11) close and shake for two minutes;

12) shake for one-minute spells every 15 minutes, up until the PVC is solubilized;

13) pour the mixture into an covered evaporation dish and leave in a quiet place;

14) wait until the film is completely formed;

15) remove the film from the dish and leave it in a dark place.

If the film is to be made directly on the plug, proceed up until point 12 above and then deposit 64 microlitres of the mixture obtained directly on the centre of the lower face of the plug. Then wait until the mixture has completely evaporated.

The inert membrane 13 can be made using the same process as the membrane 12, with the only difference being that operation no. 4 above will be excluded, so that no ion carrier is introduced.

Claims.

1. A biomedical monitoring apparatus and a sensor for monitoring ionic activity in biological fluids, comprising:

- a length of plastic tube (6) insertable in a circulation circuit of a biological fluid, in which tube (6) one or more pairs of electrodes (10) are inserted, each pair comprising a first electrode (10a) connected to a sensor (12) contacting the biological fluid and a second electrode (10b) connected to an inert membrane (13) placed in direct contact with the biological fluid;
- one or more sensors (12) in each containing a carrier matrix solution of ions, the ions being of a type which coincides with the ion type to be monitored;
- a data processing unit (4) receiving electrical signals coming from at least two said electrodes (10) inserted in the plastic tube (6), said unit (4) being specially set up in order to translate said electrical signals into a numerical value of

ionic activity and to visualize said signals in alphanumeric and/or graphic form.

2. An apparatus as in claim 1, characterised in that each sensor has a membrane conformation.

3. An apparatus as in claim 1, characterised in that the plastic tube (6) comprises one or more pairs of projections (7) each being provided with a through hole in which a conical plug (8) is inserted; one electrode (10) being implanted inside each conical plug (8); each of which conical plugs (8) supports a membrane (12) and an inert membrane (13) in such a way that the membranes are in contact with the fluid to be analyzed as well as with the electrode (10).

4. An apparatus as in claim 1, characterised in that the data processing unit comprises means for calibrating the apparatus by an insertion into the biological fluid of a liquid having a preestablished sample ionic concentration.

5. A process for obtaining a sensor to be inserted in an apparatus of the preceding claims,

characterised in that it comprises the following phases:

preparation of a PVC solution in a solvent suitable for solubilizing both the PVC and an additive matrix solution;

mixing the PVC solution with a carrier matrix solution for a predetermined ion;

depositing the mixture in an evaporation dish for a time necessary for complete evaporation of the mixture, thus obtaining a PVC film containing an element which is sensitive to ionic activity.

6. A process as in claim 5, characterised in that in the final phase the mixture is deposited in preestablished doses directly on a lower face of the plug (8) and formation by evaporation occurs directly on said lower face.

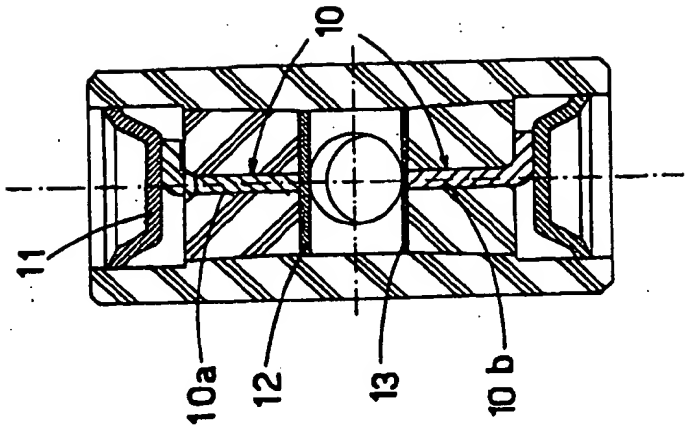


FIG.2

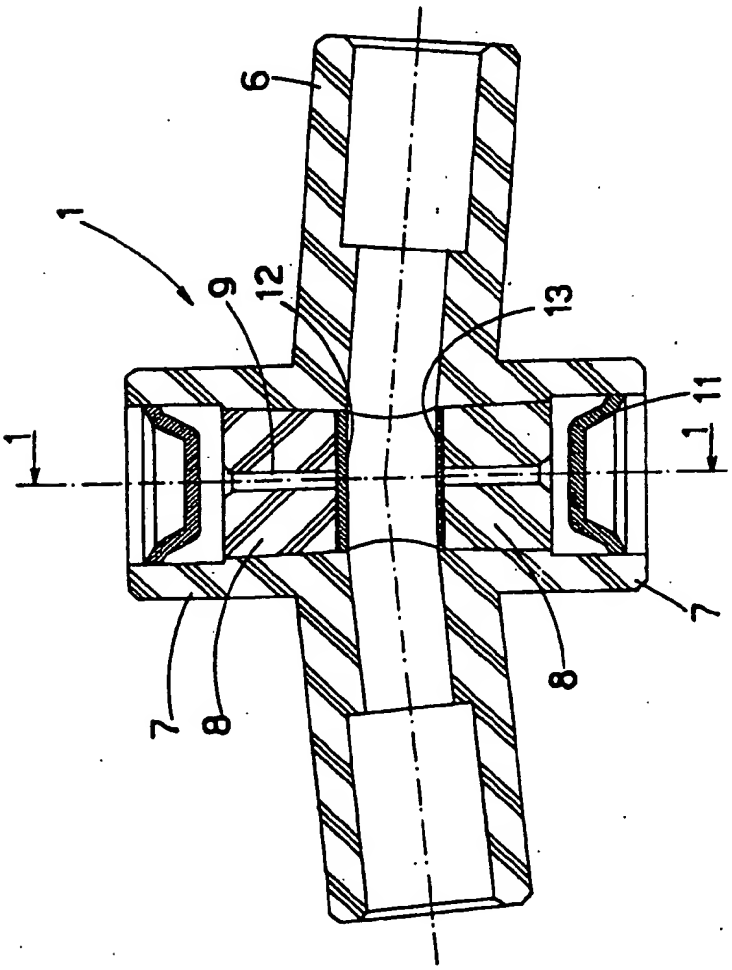
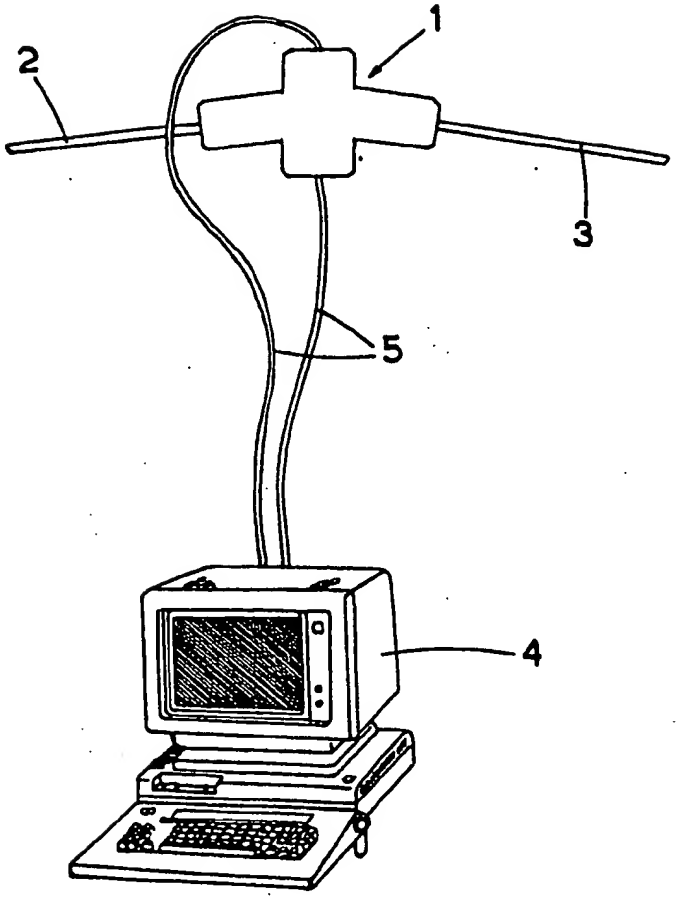


FIG.1

FIG. 3



INTERNATIONAL SEARCH REPORT

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PCT/IT 94/00028

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N27/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 791 932 (MARGULES) 20 December 1988 see column 3, line 13 - column 5, line 28 see figures	1
A	---	2,3
A	WO,A,91 01495 (PUBLIC HEALTH LABORATORY SERVICE BOARD) 7 February 1991 see page 7, line 7 - page 8, line 13 see page 10, line 5 - line 24 see figures 1,2	1,2

A	EP,A,0 102 042 (KABUSHIKI KAISHA TOSHIBA) 7 March 1984 see page 5, line 2 - page 12, line 9 see figures	1,2,6

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 04868 (WONG) 2 April 1992 see page 1, line 9 - page 5, line 11 see page 10, line 8 - page 19, line 15 see figures ---	1,2,4
A	WO,A,87 00286 (ILEX CORPORATION) 15 January 1987 see page 18, line 12 - page 21, line 22 see page 25, line 1 - page 31, line 20 see figures 1-4A ---	1,2,4,5
A	TRENDS IN ANALYTICAL CHEMISTRY, vol.2, no.2, February 1987, AMSTERDAM, NL pages 46 - 49 DIAMOND ET AL. 'In vivo sensors' see page 46, left column, line 46 - page 48, left column, line 8 see figure 1 -----	1,2,4-6

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INTERNATIONAL SEARCH REPORT

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PCT/IT 94/00028

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4791932	20-12-88	NONE		
WO-A-9101495	07-02-91	AU-B-	639005	15-07-93
		AU-A-	5944490	22-02-91
		EP-A-	0483291	06-05-92
		JP-T-	4506864	26-11-92
		US-A-	5312537	17-05-94
EP-A-0102042	07-03-84	JP-C-	1606855	13-06-91
		JP-B-	2033981	31-07-90
		JP-A-	59038647	02-03-84
		DE-A-	3376762	30-06-88
		US-A-	4533457	06-08-85
		US-A-	4647362	03-03-87
WO-A-9204868	02-04-92	US-A-	5165406	24-11-92
		EP-A-	0505530	30-09-92
WO-A-8700286	15-01-87	AU-B-	602868	01-11-90
		AU-A-	6124486	30-01-87
		CA-A-	1257331	11-07-89
		EP-A-	0230449	05-08-87
		JP-T-	63500539	25-02-88